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Recent applications of olefin metathesis and related reactions in carbohydrate chemistry

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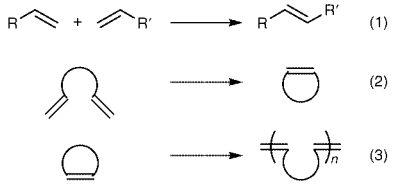
The potential use of olefin metathesis reactions in carbohydrate chemistry is discussed. In recent years, the use of olefin metathesis reactions for the construction of carbon–-carbon bonds has significantly expanded with the development of efficient and well-defined catalytic systems (1–7). These catalytic systems have found extensive use through cross-metathesis, ring-closing metathesis and ring-opening metathesis reactions for the syntheses of many carbohydrate-containing natural products. In some cases it has been shown that carbohydrate molecules can be synthesized from non-carbohydrate precursors using this simple but efficient procedure.

Professor René Roy was born in Sherbrooke, Québec, Canada in 1952. He received his Ph.D. degree in medicinal chemistry with Professor Stephen Hanessian in 1980 at the University of Montreal. He then obtained an NRC fellowship from 1980–1985 and worked in the Biological Sciences Division of the National Research Council in Ottawa, Ontario where he conducted immunological studies with Dr H. J. Jennings on bacterial polysaccharide vaccines. From 1985 onward, he joined the Department of Chemistry of the University of Ottawa were he moved to the rank of full Professor in 1995. During that time he also became adjunct Professor to the Department of Microbiology and Immunology. His research interests are centered around neoglycoconjugate syntheses and their applications in carbohydrate–protein interactions related to cancer vaccines and flu virus infections. He developed the first syntheses of glycodendrimers as potential antiadhesins. He made several contributions towards glycopolymer synthesis and their applications as coating antigens in ELISA assays. His recent interests lie in transition metal catalyzed reactions and phytomedicines. He has received the Hoffmann-La Roche Limited award in 1997.

Dr Sanjoy Kumar Das was born in Raiganj, India, in October 1967. He received his M.Sc. degree in Organic Chemistry from North Bengal University in 1991. After completing his Ph.D. degree under the supervision of Dr Mukund K. Gurjar at the Indian Institute of Chemical Technology, Hyderabad, India in 1996, he joined Professor Pierre Sinaÿ's laboratory at École Normale Supérieure, Paris as a postdoctoral fellow. After spending two years in Paris, he moved to Professor Roy's laboratory where currently he is working as a postdoctoral fellow. He is the recepient of several awards (awarded medals in B.Sc. and M.Sc. Exams. and selected as a best research scholar during his Ph.D. in 1995) including the most prestigious, Council of Scientific and Industrial Research, New Delhi, award. His research interests include the transition-metal catalyzed syntheses of neoglycoconjugates and the development of new methodologies in carbohydrate chemistry.

Introduction

The use of olefin metathesis in organic synthesis has grown considerably in recent years.[1,2] This simple procedure does not require the use of any additional reagents except for a catalytic amount of metal carbene, and the only by-product that forms is volatile ethylene gas. The importance of this carbon–carbon bond construction method is evident from the huge number of publications that have appeared within a short span of time.[3–5] Olefin metathesis can be categorized into three different sections: (1) cross-metathesis, in which two different alkenes undergo an intermolecular transformation to form a new olefinic product (eqn. 1); (2) ring-closing metathesis, a procedure which is useful for the formation of cyclic compounds (eqn. 2); and (3) ring-opening metathesis polymerization, which involves the metathetic opening of strained cyclic olefins to give polymeric compounds (eqn. 3).



Although many examples of cross-metathesis, ring-closing metathesis and ring-opening metathesis reactions are available in the literature, only carbohydrate-related applications reported up to September 1999 will be discussed herein. Some interesting discoveries (cyclotrimerization, isomerization) from our laboratory using Grubbs' catalyst will also be discussed.

Catalyst development

The early examples of olefin metathesis employed classical catalysts which usually included a tungsten chloride or oxychloride and an alkyl metal species. These catalysts were less reactive to olefins due to their increased stability and yields were generally found to be low.[6–8] The other established catalyst is dichlorobis(2,6-dibromophenoxy)oxotungsten, $Cl_2(ArO)_2W{=}O$.[9] Although this system shows good functional group tolerance and has been used for many syntheses, it is considered to be unsuitable for industrial applications owing to its complexity and cost. Olefin metathesis began to receive more attention in 1993, when Basset and co-workers developed and applied the tungsten catalysts **1** and **2** for cross-metathesis reactions.[10,11] To date, these have been successfully shown to be remarkably tolerant to heteroatoms, including sulfur, silicon, phosphorus, and tin. Since the use of this catalyst is limited because of its steric demand toward shorter alkenes, such as allyl groups, researchers have searched for alternative catalytic systems for olefin metathesis reactions. One of the most useful catalysts for olefin metathesis reactions is the molybdenum catalyst (**3**) developed by Schrock *et al.*[12] Although the major advantage of **3** is its high reactivity towards a broad range of substrates with a variety of functional groups, this catalyst also

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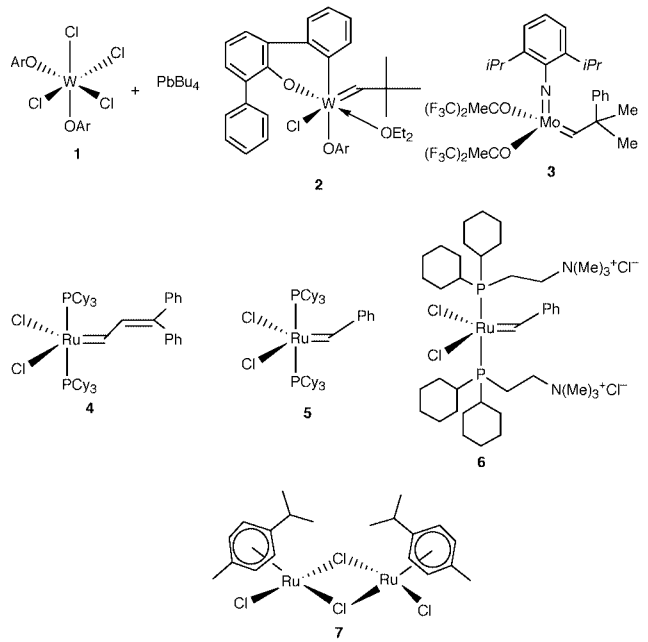
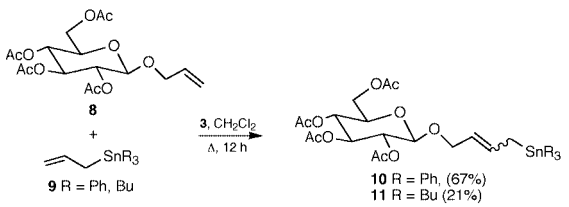


has some limitations. Its major drawbacks are that it is air sensitive and has moderate to poor functional group tolerance. Much work on the development of catalytic systems has been done by Grubbs and co-workers using two very important ruthenium-based catalysts, **4**[13] and **5**.[14] Although both catalysts benefit from the same impressive tolerance to air, moisture and various functional groups, catalyst **5** provides improved initiation rates and can be prepared easily. In addition to the catalytic systems discussed above, a few other transition metal catalysts have been prepared for olefin metathesis reactions. Among them, the water soluble ruthenium catalyst **6**,[15] also developed by Grubbs and co-workers, and a photoinducible dichloro(*p*-cymene)ruthenium(II) dimer (**7**), developed by Fürstner and Ackermann,[16] are noteworthy. Many applications of these catalysts have been recently reported in the literature. Although several metal carbenes have been mentioned, we have endeavoured to cover only the catalytic systems which have been used in carbohydrate chemistry.

Cross-metathesis

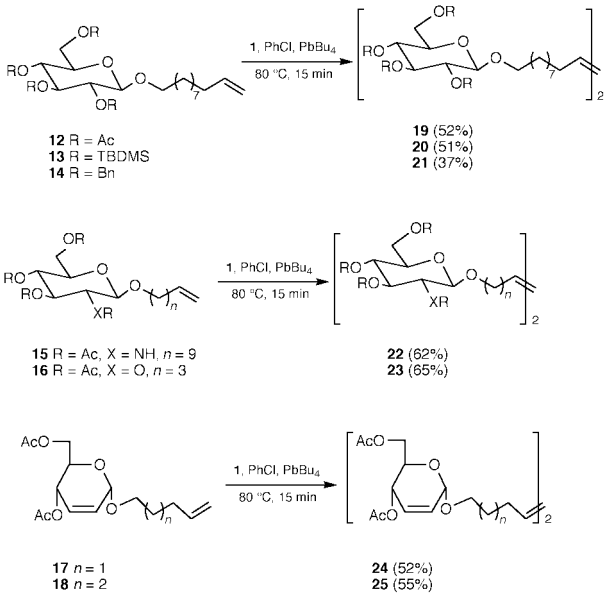
The cross-metathesis reaction, in which two different alkenes are used to form a new alkene, is shown in eqn. 1. This method has not found widespread application because of the fact that general conditions which give rise to high yields and stereoselectivity have not yet been discovered. With the development of new, well-defined metal alkylidenes and a better understanding of the nature of the reaction mechanisms involving these catalysts, some examples of selective cross-metathesis reactions have recently appeared in the literature. Thus, Blechert *et al.*[17] have shown that allyltributyl or allyltriphenyl stannane can undergo selective cross-metathesis reactions with allyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (**8**) using Schrock's catalyst **3** (Scheme 1). The cross-metathesized



Scheme 1

product **10** could be very useful for nucleophilic additions to electrophilic carbon centres and for radical reactions.

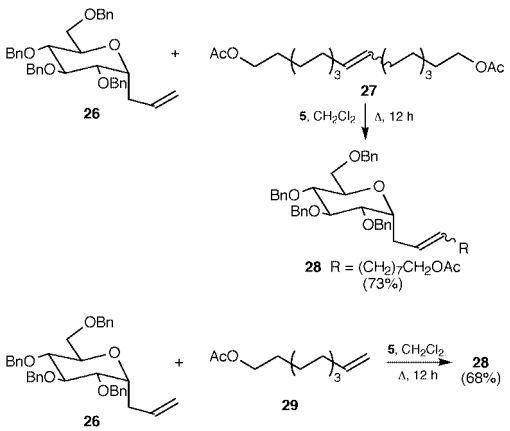
Descotes *et al.*[18] have chosen this procedure as the most efficient method for the preparation of sugar bolaamphiphiles (**19**–**25**) in good yields (Scheme 2). Glucosides protected as



Scheme 2

acetates (**12**) or silyl ethers (**13**) were found to be superior substrates to benzyl-protected carbohydrates (**14**) in metathesis reactions. The same group has also successfully extended this methodology to the *N*-acetyl aminosugar **15**. Catalysts **1** and **2** were found to be active with pentenyl glycosides, whereas allyl glycosides did not afford any metathesis products; again the catalysts were deactivated by competitive coordination of the ether oxygen to the metallocarbenes. Metathesized products were synthesized in good yields, but the *cis*:*trans* ratios were not determined.

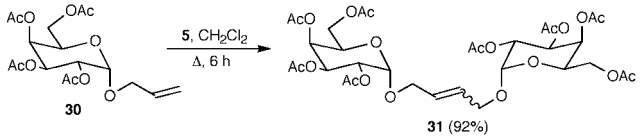
Recently, Grubbs *et al.*[19] have used the cross-metathesis reaction between *C*-allyl α-D-glucopyranoside and disubstituted olefins to supress the formation of self-metathesis products (Scheme 3). Homodimer **27** was subsequently used to function-



Scheme 3

alize *C*-allylglycoside (**26**) in 73% yield as a mixture of *cis* and *trans* isomers in a 3:1 ratio. In order to compare the yield and isomeric ratios, they performed the reaction with 4 equiv. of the terminal olefin **29**. The cross-metathesized product **28** was isolated in a marginally lower yield with slightly lower *trans*-selectivity (68%, 2.2:1 *E*:*Z*).

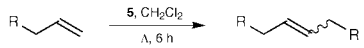
We have shown that peracetylated *O*-allyl β-galactoside (**30**) can be easily homodimerized in the presence of Grubbs' or Schrock's catalyst (Scheme 4).[20] Since, in both cases, the yields were found to be more or less the same, catalyst **5** was preferred

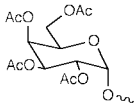
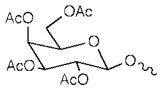
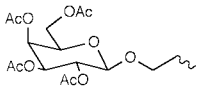
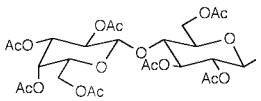
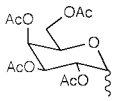
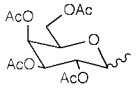
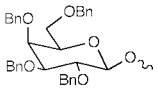


Scheme 4

because of its operational simplicity. Various other homodimers were synthesized using the same catalyst **5** (Table 1).

Table 1 Olefin self-metathesis of alkenyl *O*- and *C*-glycopyranosides

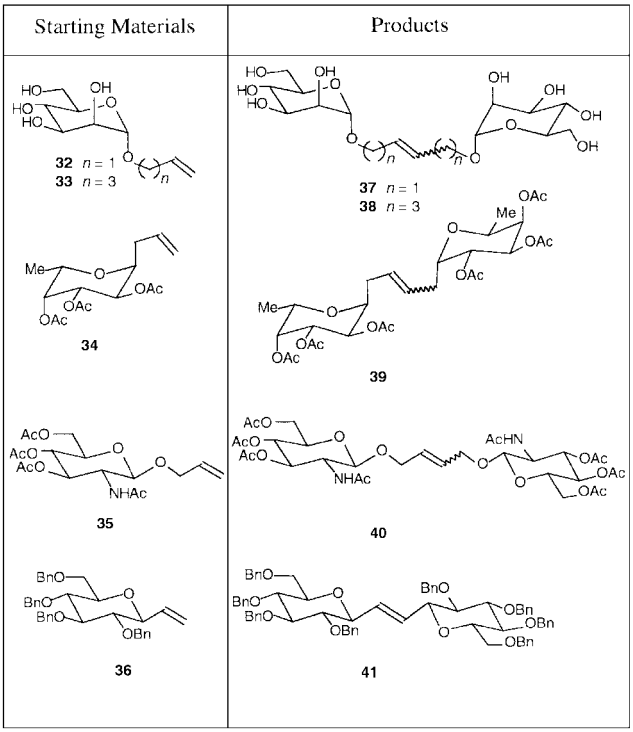


R	Product (*E*:*Z*)	Yield (%)
	(5:1)	92
	(4:1)	95
	(5:1)	85
	(4:1)	89
	(2:1)	82
	(1:1)	75
	(3:1)	76

In order to investigate the influence of unprotected glycosides in metathesis reactions, we have shown[21] that the reaction proceeds smoothly with catalyst **5** at room temperature rather than under refluxing conditions, where *O*-allyl (**32**) and *O*-pentenyl mannopyranosides (**33**) gave homodimers **37** and **38** in good yields. Compounds **34** and **35** also provided homodimers, **39** and **40** in 95 and 66% yields, respectively (Scheme 5). The sterically more demanding C-vinyl glycoside (**36**) can undergo olefin metathesis reaction at elevated temperatures (70 °C) albeit slowly (Table 2).

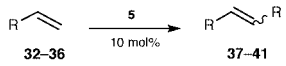
Olefin metathesis has also been used for the synthesis of divalent sialoside derivatives.[22] Treatment of allyl *O*-α-sialoside (**42**) with 5 mol% of Grubbs' catalyst (**5**) in refluxing dichloromethane gave homodimer **44** in 82% yield. The corresponding thio-analogue, **43**, gave homodimer **45** in only 26% yield. Undoubtedly, the lower yield was due to catalyst-poisoning by the sulfide moiety (Scheme 6).

Synthesis of *O*- and *C*-glycosides **30** and **46** with differently functionalized spacers in the aglycon moiety was also carried out by cross-metathesis reactions from *O*-allyl and *C*-allyl glycosides in good yields (Table 3).[23] These extended glycosides can be further transformed by known methods into useful neoglycoconjugates including glycodendrimers and polymers. An interesting application of this reaction was the synthesis of

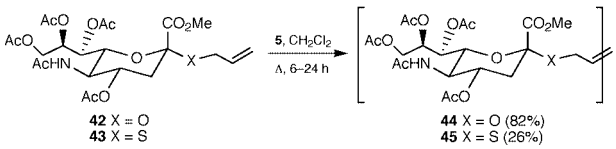


Scheme 5

Table 2 Olefin self-metathesis of alkenyl *O*- and *C*-glycopyranosides



Substrate	Product	Reaction conditions	Yield (%)	*E*:*Z* Ratio
32	**37**	CH_2Cl_2:MeOH (3:1); rt	60	1.7:1
32	**37**	CH_2Cl_2:MeOH (3:1); 40 °C	34	1.4:1
33	**38**	CH_2Cl_2:MeOH (3:1); rt	67	1.3:1
33	**38**	CH_2Cl_2:MeOH (3:1); 40 °C	42	1.1:1
34	**39**	CH_2Cl_2; reflux	95	3:1
35	**40**	CH_2Cl_2; reflux	66	5:2
36	**41**	CH_2Cl_2; rt	n.r.	—
36	**41**	CH_2Cl_2; reflux	8	100:0
36	**41**	$ClCH_2CH_2Cl$; 70 °C	24	100:0



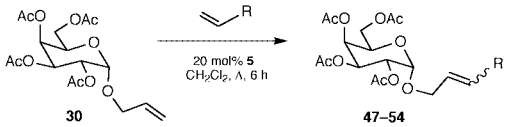
Scheme 6

C-linked pseudodisaccharides, which can be synthesized by the cross-metathesis between two different sugar moieties, using a head to tail condensation procedure (Scheme 7 and Table 4).

The cross-metathesis of *O*- or *C*-allyl glycosides and *N*-alkenyl-containing oligosaccharide derivatives (peptoids) has been reported by Hu and Roy.[24] The treatment of a GlcNAc derivative (**35**) with *N*-allylamine in the presence of Grubbs' catalyst (**5**) gave no cross-metathesis product, but dimerization of **35** was achieved in 30% yield. Alternatively, the use of amine **61** in the cross-metathesis reaction with **35** gave **62** in 41% yield. This was a surprising result, since free carboxylic acids are not considered to be good substrates for olefin metathesis reactions (Scheme 8).

The cross-metathesis reaction involving polymer-bound olefins has more potential benefits because product isolation should be easier. In an interesting application of the cross-metathesis reaction on a solid support, Blechert *et al.*[25] have

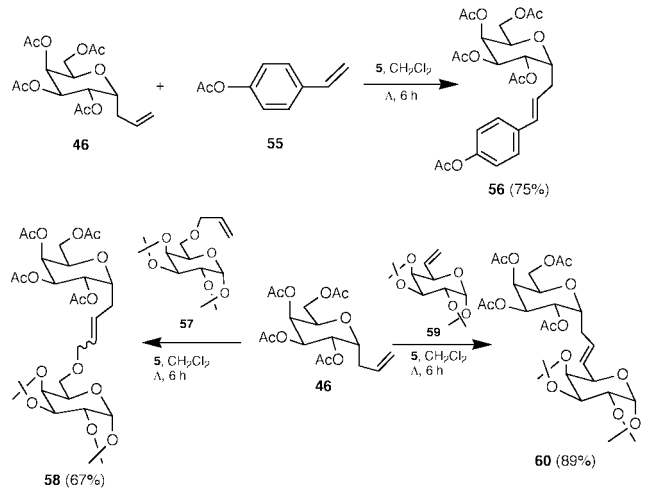
Table 3 Isolated yields and *E*:*Z* ratios of ruthenium catalyzed cross-metathesis of **30** with alkenes **47–54** to provide extended glycosides



30 **47–54**

Entry	R	Equiv.	Reaction conditions	Product	Yield (%)	*E*:*Z* Ratio
1	CH_2SiMe_3	2	A	**47**	94	4:1
2	$CH_2CH_2CO_2Me$	2	A	**48**	67	2:1
3	CH_2OTBS	2	A	**49**	69	95:5
4	Ph	2	A	**50**	60	90:10
5	Ph	4	A	**50**	80	97:3
6	p-AcOPh	4	A	**51**	75	95:5
7	$(CH{=}CHCH_2OAc)_2$	2	A	**52**	70	5:1
8	CH_2NHBoc	2	A	**53**	30	4:1
9	CH_2NHBoc	2	B	**53**	57	4:1
10	CH_2NHCbz	2	A	**54**	39	4:1
11	CH_2NHCbz	2	B	**54**	65	4:1

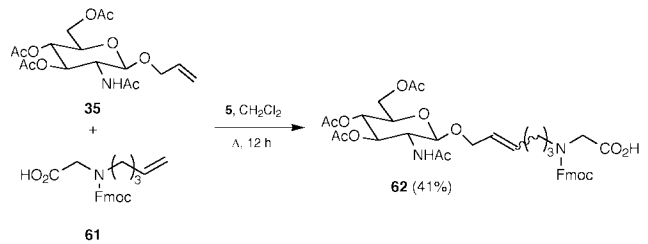
Method A: CH_2Cl_2, reflux, 6 h; **Method B**: CH_2Cl_2; rt, 15 h



Scheme 7

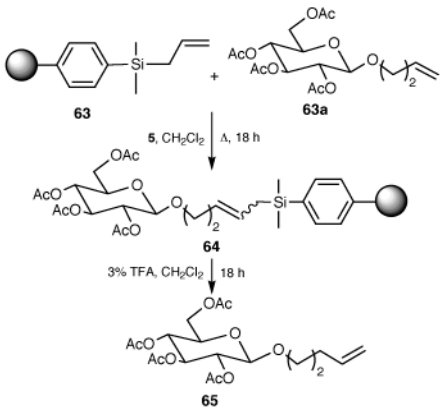
Table 4 Isolated yields and *E*:*Z* ratios of ruthenium catalyzed cross-metathesis of a *C*-allyl galactoside derivative (**46**) with alkenes **55, 57** and **59**

Entry	Starting material	Equiv.	Product	Yield	*E*:*Z*ratio
1	**55**	2	**56**	50	100:0
2	**55**	4	**56**	75	100:0
3	**57**	2	**58**	67	4:1
4	**59**	2	**60**	89	2:1



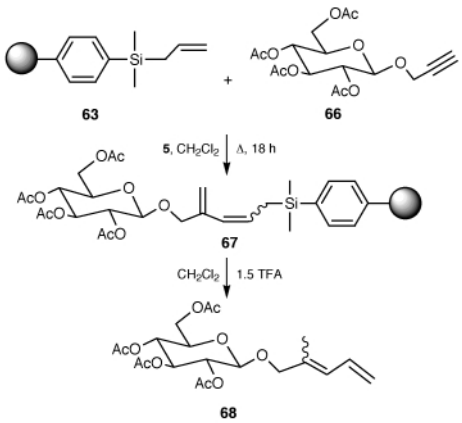
Scheme 8

reported the metathesis reaction between immobilized allyl silane **63** with various olefins (*e.g.*, **63a**) to give new immobilized olefins. Product **64** could be cleaved under acidic conditions to provide the homologated derivative **65** (Scheme 9).



Scheme 9

In another solid-support application, Schuster and Blechert[26] have reported a catalytic cross-coupling reaction between the functionalized terminal alkynes **66** and allylsilyl polystyrene, **63**, *via* a more selective ruthenium-catalyzed crossed yne–ene metathesis reaction. Upon cleavage of **67** by 1.5% TFA, the procedure afforded the 1,3-diene **68** (Scheme 10).



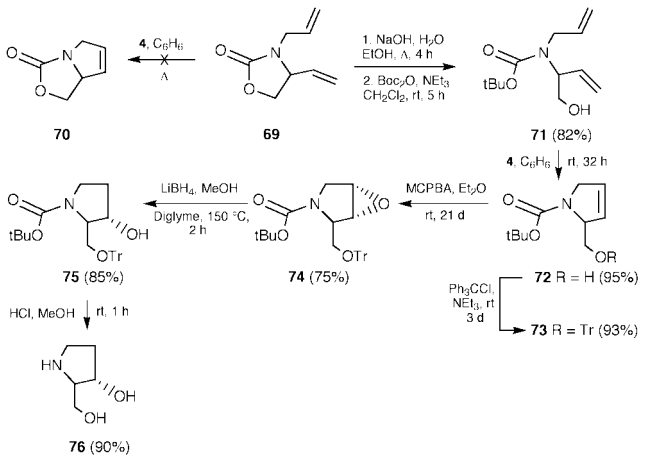
Scheme 10

Ring-closing metathesis

Among all the categories, ring-closing metathesis (RCM) reactions, which lead to cyclic products, have found the widest application in synthesis. With the advent of well-defined molybdenum- and ruthenium-based catalysts, high yielding

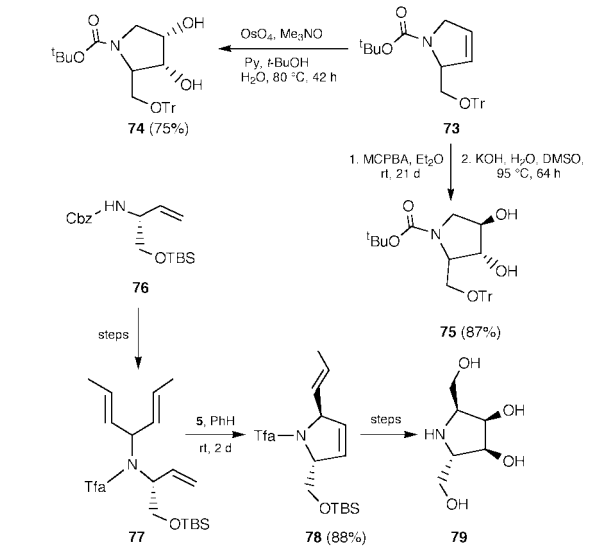
RCM of smaller ring systems was realized. It has been successfully used for the synthesis of a variety of carbo- and heterocyclic products and has also proven to be the key step for many total syntheses.

Huwe and Blechert[27] have chosen this novel strategy for the synthesis of azasugars from vinyl glycine methyl ester using catalyst **4**. They have shown that compound **69** is not suitable for olefin metathesis reactions (Scheme 11). Hydrolysis of **69** with NaOH in aqueous ethanol and subsequent treatment with di-*tert*-butyldicarbonate [$(Boc)_2O$] gave **71**. Olefin metathesis of **71** with 4 mol% of catalyst **4** gave a good yield of the RCM product **72** (95%). Compound **72**, on subsequent epoxidation and hydride opening of the epoxide, gave the 1,2-dideoxy sugar **76**.



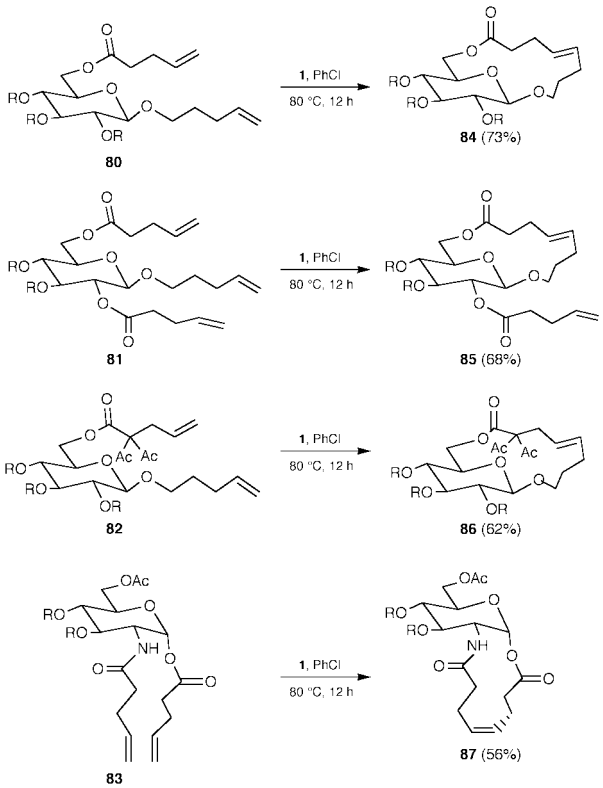
Scheme 11

In an another application, the same group[28] applied the Sharpless dihydroxylation method to obtain 1-deoxy azasugars (*e.g.*, **74** and **75**). They also used an analogous strategy toward the synthesis of the homoazasugar **79** from vinyl glycine methyl ester (Scheme 12).



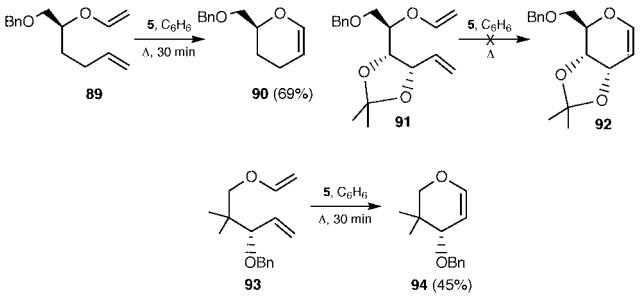
Scheme 12

Descotes *et al.*[29] have used catalysts **1** and **2** for an intramolecular carbohydrate macrocyclization. Thus, diluted solutions of the unsaturated substrates **80**–**83** in chlorobenzene when treated with 7 mol% of catalyst **1** at 80–85 °C afforded the cyclic products **84**–**87** in reasonable yields (56–73%). It has been observed that homodimerization of the starting material did not occur during the metathesis reaction. The results of the metathesis reaction are summarized in Scheme 13. The cyclization took place between the substituents at C1 and C6 which are in a *cis*-configuration. Thus, the chemoselectivity of the reaction could be controlled by the anomeric configuration.



Scheme 13

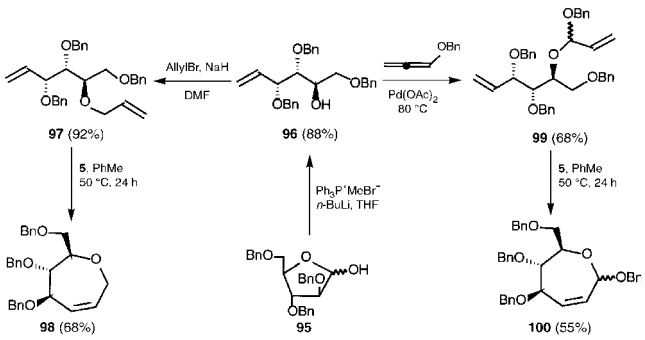
Sturino and Wong[30] have made some interesting observations. They have reported the ring-closing metathesis of the vinyl ethers **89**, **91** and **93** with Grubbs' catalyst (**5**) (Scheme 14). Although compound **89** gave the cyclic product **90** in 69% yield, compound **91** was inert. They concluded that the presence of an allylic alkoxy substituent has a negative influence on the RCM reaction. As an exception to this finding, it was shown that compound **93** can give **94** due to the Thorpe–Ingold effect of the *gem*-dimethyl substituents.



Scheme 14

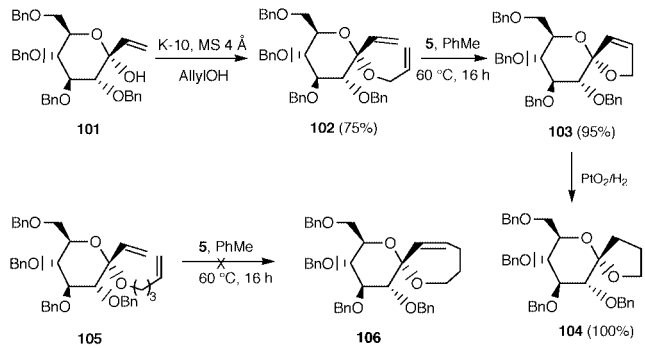
A novel and versatile route to highly functionalized chiral oxepines, which is based on RCM of differently protected glycofuranoses,[31] has been developed by van Boom *et al.* Thus, treatment of **97**, which can be easily prepared from 2,3,5-tri-*O*-benzyl-D-arabinofuranose (**95**), with 5 mol% of the Ru-catalyst **5** in toluene at 50 °C for 24 h gave the expected cyclized product, **98** (Scheme 15). The success of this smooth cyclization of the vinyl-*O*-allyl derivatives encouraged this group to prepare interesting oxepanes, such as **100**. The RCM of **99** led to the formation of **100** as a mixture of diastereoisomers (1:1) in 55% yield. These compounds are potentially useful synthons for the construction of higher carbon sugars.

Recently, it has been shown[32] that the RCM reaction can be used as a highly stereoselective route to unsaturated spiroacetals



Scheme 15

starting from a terminal alkene–*O*–alkene arrangement at the anomeric centre of a sugar. Thus, the reaction of **102** in the presence of Grubbs' catalyst (**5**) (6 mol%) at 60 °C for 16 h gave the 1,6-dioxa-(5*R*)-spiro(4,5)dec-3-ene derivative **103** in excellent yield (95%) (Scheme 16). Interestingly, it has also been



Scheme 16

shown that similar treatment of diene **105** did not lead to the expected spiro compound, **106**. Instead, a dimeric product was isolated. The formation of this dimer could not be prevented by lowering the concentration of the substrate with a larger amount of catalyst. It has been concluded that the RCM reaction depends on the site of the ring closure rather than the ring size.

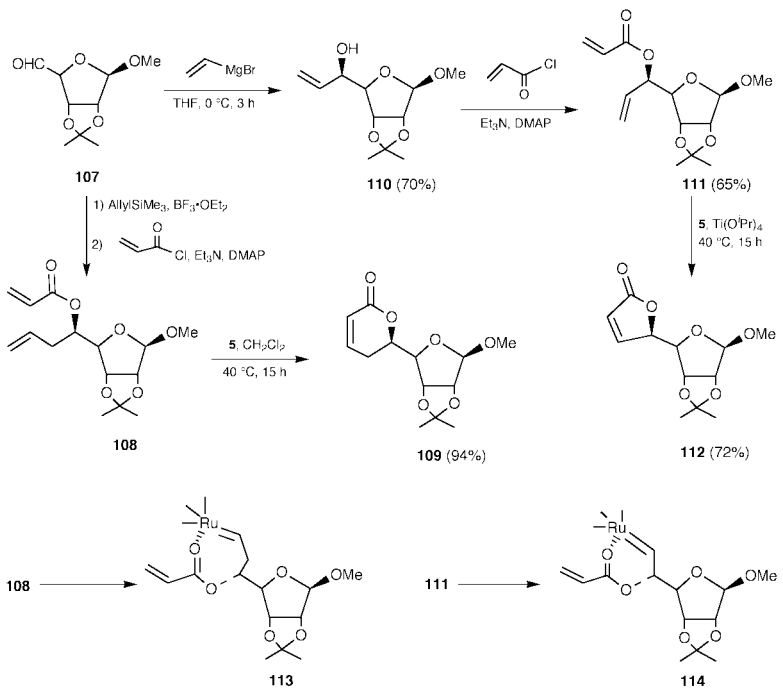
The ring-closing metathesis of the acryloylated derivatives **111** and **108**, derived from allylic and homoallylic alcohols, appeared conveniently poised to provide five or six-membered α,β-unsaturated lactones (**109** and **112**). Unfortunately, this scenario did not happen to be operational. It could be postulated that this is due to the formation of unproductive six- (**114**) and seven-membered (**113**) metal chelates, formed between the ester carbonyl and the intermediate carbene species. These intermediates were apparently too stable for the subsequent olefin metathesis reactions to occur.[33]. However, Ghosh and his co-workers[34] have successfully overcome this problem by adding the external Lewis acid [Ti(^{i}OPr)$_4$], which can disrupt such inactive complexes and can provide effective cyclization. These methods provide convenient access to α,β-unsaturated, γ and δ-lactones (**109** and **112**) in good yields (Scheme 17).

The RCM reaction is an important method for the preparation of carbohydrate derivatives. Recently, Evans and Murthy[35] have developed an interesting silicon-tethered ring-closing metathesis procedure for the synthesis of C_2-symmetrical 1,4-diols (**115**) (Scheme 18). Dihydroxylation of the cyclic alkene by the Sharpless-protocol and removal of the protecting groups afforded the reduced carbohydrate D-altritol (**118**).

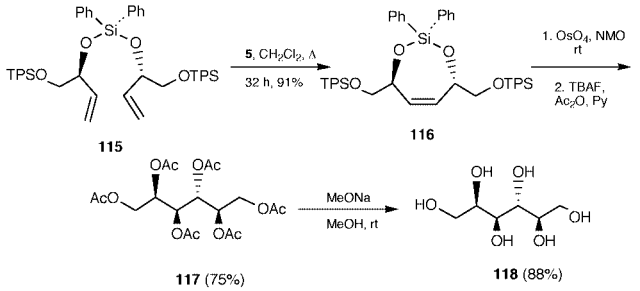
Overkleeft *et al*.[36] reported an efficient synthesis of pyrrolizidine (**121**) and quinolizidine (**125**) azasugar derivatives by using catalyst **4** or **5**. When γ-lactam **120**, derived from aldehyde **119** by Wittig olefination, was subjected to an RCM reaction with catalyst **4**, the expected 5/5 bicyclic pyrrolizidine azasugar (**121**) was formed (Scheme 19). Although the reaction required prolonged reaction time and elevated temperature (50 °C), compound **121** was still isolated in 66% yield. In other examples, the quinolizidine derivative **125** could be derived from either **122a** or **122b** using catalyst **4** or **5**.

The same group[37] has reported a formal total synthesis of the important glucosidase inhibitor castanospermine **130** using olefin metathesis as a key step. It is noteworthy that the cyclization of diene **126**, which contains an α,β-unsaturated ester (not usually suitable for metathesis reactions), reacted with catalyst **4** to give the bicyclic lactam **127** in 70% yield (Scheme 20).

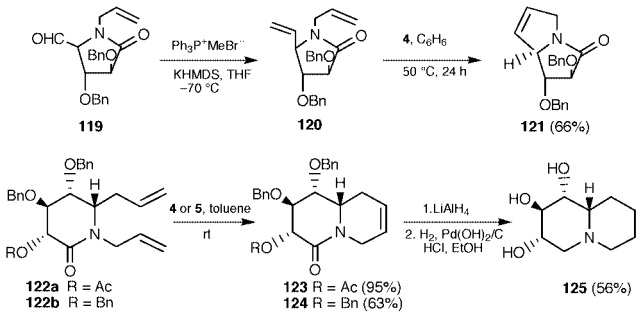
In the synthesis of *C*-aryl glycosides, Schmidt and Sattelkau[38] have used the RCM strategy as the key step (Scheme 21). An interesting feature of their approach was that protecting



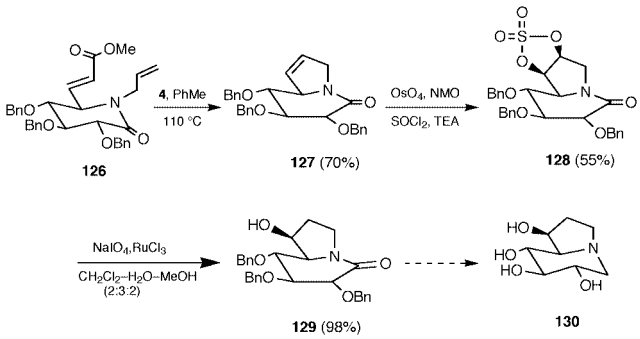
Scheme 17



Scheme 18

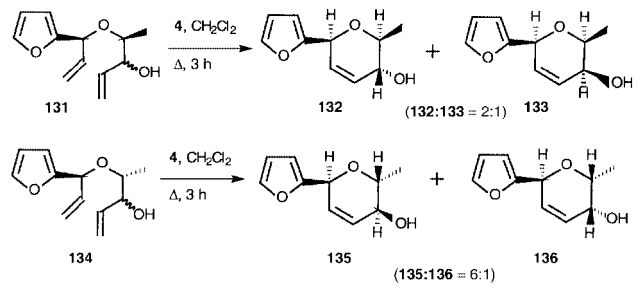


Scheme 19



Scheme 20

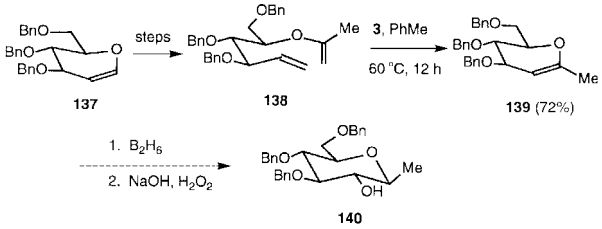
groups, normally necessary for *C*-glycoside synthesis, were not required for the success of the reaction.



Scheme 21

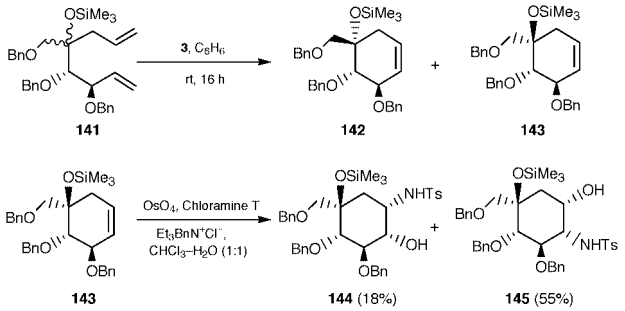
Another approach toward the synthesis of *C*-glycosides was reported by Calimente and Postema,[39] in which RCM was employed as a key step for the intramolecular cyclization. The starting material, **138**, was prepared from the corresponding glycal, **137**, in a few steps. Exposure of the acyclic enol ether **138** to catalyst **3** in toluene solution produced the *C*-linked glycal **139** in 72% yield. It was further suggested by the authors[39] that glycal **139** could then be easily converted into a *C*-glycoside (**140**) by an oxidative hydroboration (Scheme 22).

An efficient and practical method for the preparation of valiolamine has been described.[40] The starting material, **141**, was easily prepared from a D-arabinose derivative and the ring-



Scheme 22

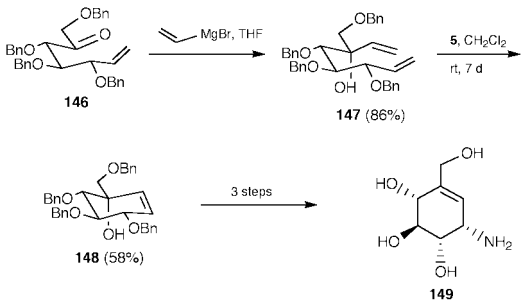
closing metathesis reaction proceeded smoothly (92% crude yield) to provide the substituted cyclohexene derivatives **142** and **143** as a 7:3 mixture of stereoisomers that could be separated by HPLC (Scheme 23). Interestingly, when the



Scheme 23

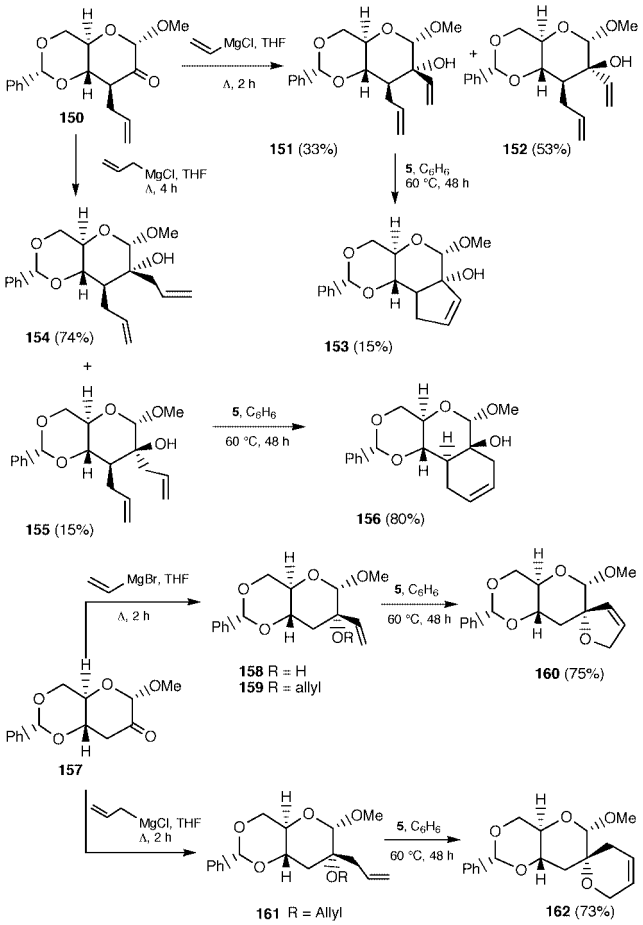
reaction was subjected to the RCM conditions using Grubbs' catalyst, the reaction failed, but proceeded effectively using Schrock's catalyst at room temperature. After separation of both isomers, compound **143** was subjected to a *cis*-aminohydroxylation toward the synthesis of valiolamine (**144**) and its isomer (**145**).

An efficient synthesis of (+)-valienamine from commercially available D-glucose has been reported by Vasella *et al.*[41] using a ring-closing metathesis reaction as a key step. The ring-closing metathesis of **147**, derived by vinylation of ketone **146**, was performed in refluxing CH_2Cl_2 using catalyst **5**. Compound **148** was then converted into (+)-valienamine in three steps with a 47% overall yield (Scheme 24).



Scheme 24

Five-, six- and eight-membered annulated sugars along with spiro systems can also be prepared in good yields.[42] The Grignard reaction between **150** and vinylmagnesium chloride gave two stereoisomers, **151** and **152** (Scheme 25). The ring closing metathesis reaction of **151** with catalyst **5** gave the five-membered annulated sugar **153** in only 15% yield, due to the steric hindrance from the *trans*-fused 5-6 ring system in the product. For six-membered ring annulation, the starting materials (**154** and **155**) were prepared by the Grignard reaction of **150** with allylmagnesium chloride. Thus, the reaction of **155** and **5** involved ring-closing metathesis to produce the annulated sugar derivatives **156** in 80% yield. The structures were unambiguously determined by X-ray crystallography. Clearly, there was no steric impediment to the formation of the *cis* and *trans* 6-6



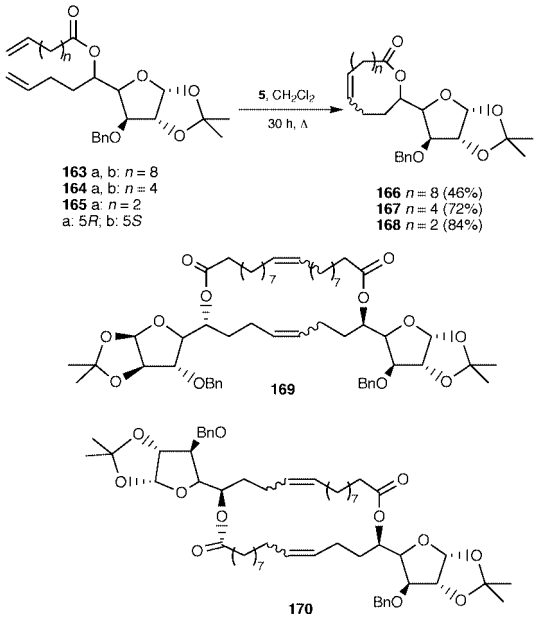
Scheme 25

ring system in both structures. Analogously, spiro-fused dihydropyran derivatives, such as **160** and **162** (Scheme 25) could also be obtained by efficient intramolecular ring-closing metathesis reactions involving allylic ethers **159** and **161**. Both derivatives were obtained from the same progenitor ketone (**157**) following the strategy described for **150** above.

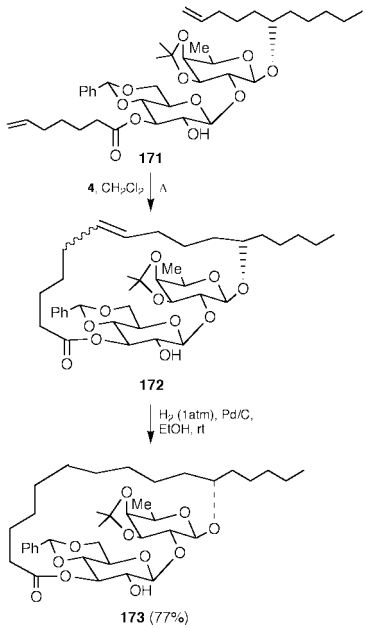
In connection with the synthesis of annonaceous acetogenins and their analogs, ring-closing metathesis of unsaturated esters (**163**–**165**) has been used toward the synthesis of 9- to 15-membered-ring lactones (**166**–**168**) in moderate to good yields (Scheme 26).[43] The RCM reaction proceeded slowly and the corresponding lactones were isolated together with *ca.* 10% of the corresponding dimers. The yield was high in the case of **168** because of the formation of a 9-membered-ring lactone. Due to polymerization, the isolated yields of the 11- and 15-membered-ring lactones were moderate. When slow syringe pump addition was carried out, the yields were slightly better, but the formation of the corresponding dimers (**169** and **170**) was not prevented.

Recently, Fürstner and Muller[44] have synthesized the disaccharide fragment of tricolorin A (**173**) *via* ring-closing metathesis as the key step (Scheme 27). Tricolorin A exhibits significant cytotoxic properties against cultured P-388 and human breast cancer cell lines. The key intermediate was prepared *via* a multistep process. When disaccharide **171** was treated with catalyst **4**, the cyclized product **172** was formed. The free hydroxy group in the substrate did not interfere with the RCM, thus illustrating again the excellent compatibility and selectivity of Grubbs' catalyst. Hydrogenation of the crude 19-membered cycloalkene (*E*/*Z* mixture) afforded the desired cyclic disaccharide **173** in 77% yield (two steps) and completed the formal synthesis of tricolorin A.

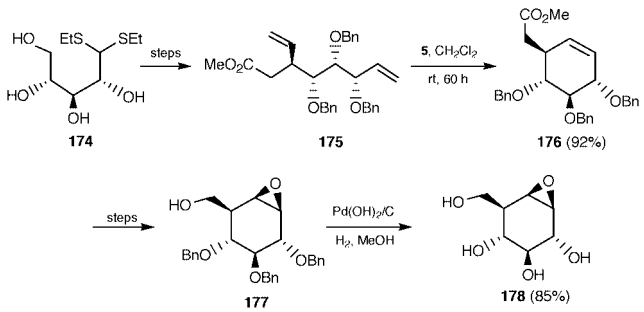
Ziegler and Wang[45] completed the direct synthesis of (+)-cyclophellitol from a carbohydrate precursor, D-xylose (Scheme 28). Ru-catalyzed ring-closing metathesis of the diene



Scheme 26



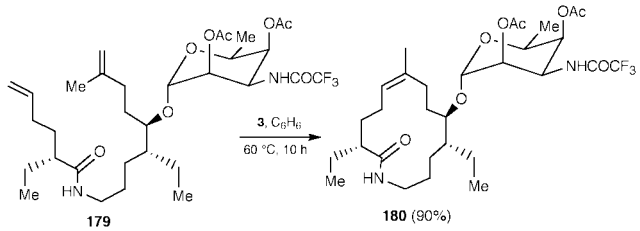
Scheme 27



Scheme 28

175 led to the efficient formation of the cyclohexene **176** in 92% yield. Compound **176** was converted to the final target (+)-cyclophellitol **178** in a few further steps.

In the enantioselective total synthesis of the antifungal agent Sch 38516 (**180**), Houri *et al.*[46] have again used the RCM reaction as the crucial step (Scheme 29). The glycoside **179** was treated with Schrock's catalyst (**3**) to provide **180** as a single cycloalkene in 90% yield.

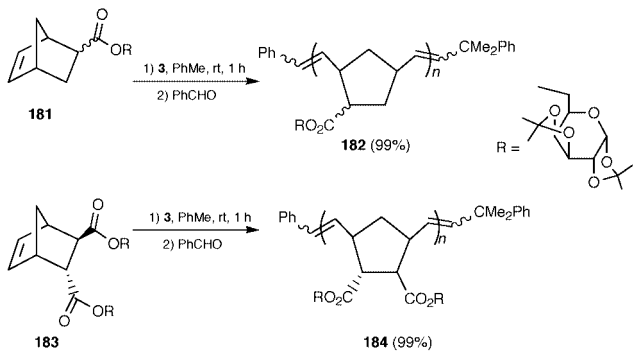


Scheme 29

Ring-opening metathesis

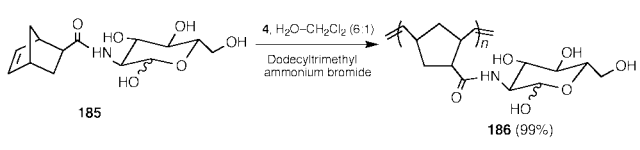
The ring-opening metathesis (ROM) reaction is a variation of the cross-metathesis reaction, where one of the olefin partners is a cyclic alkene and the driving force is the strain in the starting material that is released during the process (eqn. 3). Although this reaction is very useful in synthetic organic chemistry, the poor chemo-, stereo- and regio-selectivity have limited the synthetic utility of this reaction and, to the best our knowledge, there is no example of ROM in carbohydrate chemistry. On the other hand, in the absence of a second open-chain olefin, the metal-carbene intermediate formed by the reaction between the cyclic olefin and the catalyst can react with a series of cyclic olefins to give polymers. The application of this method (ROMP) has been greatly expanded by highly active and well-defined catalysts. Some examples of this method have appeared in the literature. A key advantage of the ROMP reaction is that the polymerization can be living, that is, the elongation can proceed more rapidly than termination or chain transfer. This living polymerization method offers new opportunities for oligomer synthesis.

Nomura and Schrock[47] have shown the formation of various kinds of norbornene-based homopolymers and multiblock copolymers (**182**, **184**) that contain protected sugars by ring-opening metathesis polymerizations of **181** and **183** using the Mo-catalyst **3**. The acetal groups in polymers containing 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose residues can be hydrolyzed rapidly under acidic conditions to afford useful water-soluble 'sugar-coated' polymers (Scheme 30).



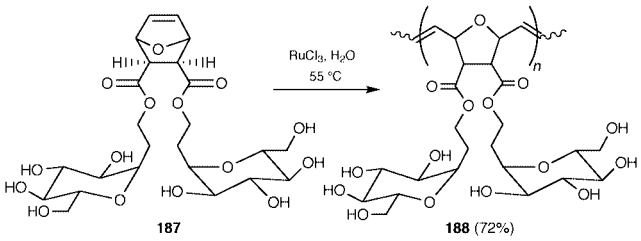
Scheme 30

The polymerization of an unprotected norbornene *N*-acylglucosamine derivative **185** has been reported in an aqueous–organic two phase system by Grubbs and Fraser[48] using catalyst **4**, since this catalyst is not sensitive to alcohol functionality (Scheme 31).



Scheme 31

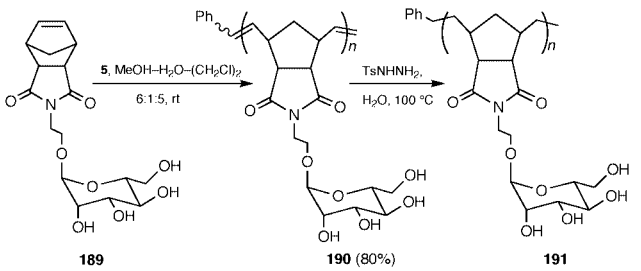
Recently, Kiessling and co-workers[49] have shown that the ROMP reaction can be used to create a polyvalent carbohydrate-bearing polymer that can block protein-initiated cell agglutination. Thus, the treatment of **187** with $RuCl_3 \cdot H_2O$ in H_2O afforded a good yield of the glycopolymer **188** (Scheme 32). This novel application of ROMP to the synthesis of



Scheme 32

polyvalent carbohydrate polymers offers new opportunities for the design of materials for modulation of cell adhesion, immobilization of particular cell types, and study of multivalency in extracellular interactions.

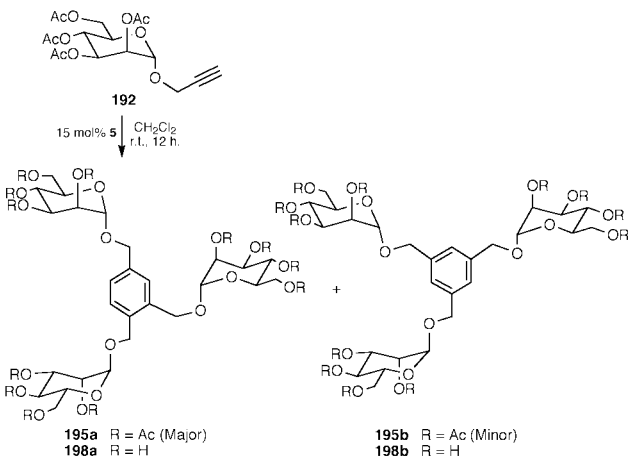
In an another application, Kiessling *et al.*[50] described ring-opening metathesis polymerization to generate collections of multivalent saccharide displays in which the number of repeat units within a set was systematically varied (Scheme 33).



Scheme 33

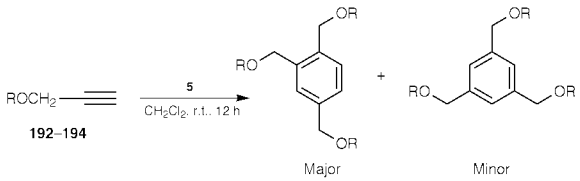
Acetylene metathesis

We have recently found that 2-propynyl glycosides can undergo a cyclotrimerization reaction in the presence of Grubbs' catalyst to give a mixture of regioisomeric aryl glycosides (Scheme 34, Table 5).[51] As oligosaccharide mimetics, such molecules may find biological utility as 'cluster-type ligands' and may help to elucidate binding specificity in multiple carbohydrate–protein interactions.

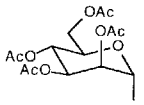
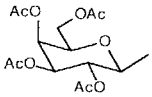
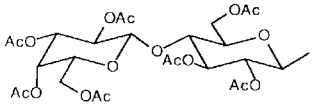


Scheme 34

Table 5 Cyclotrimerization of 2-propynyl derivatives

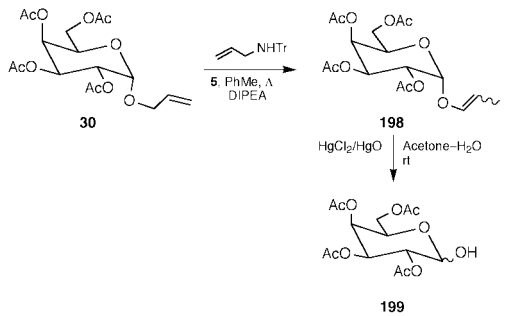


195–197

Entry	Substrate	R	Product	Yield (%)	Isomer Ratios
1	**192**		**195**	75	90 : 10
2	**193**		**196**	72	90 : 10
3	**194**		**197**	66	90 : 10

Isomerization

An unexpected[52] isomerization product, **198**, was isolated in 30% yield, instead of the anticipated cross-metathesis compound, when the cross-metathesis reaction between *N*-allyltritylamine and allyl 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranoside **30** was carried out with catalyst **5**. Furthermore, neither a sugar nor a *N*-allyltritylamine dimer could be detected. Treatment of **30** with 1,4-diazabicyclo[2,2,2]octane (DABCO) in the presence of Grubbs' catalyst (**5**) afforded only 4% of the isomerized product, **198**, together with 40% of allyl α-D-galactopyranoside homodimer. Similar results were obtained when triethylamine was used as base. Neither isomerization nor metathesis products were detected when diethylamine or pyridine were used. The isomerized product **198** was obtained with the highest yield when **30** was treated with diisopropylethylamine (DIPEA) in the presence of Grubbs' catalyst (**5**). However, all the isomerization yields of these reactions were still very low in the absence of *N*-allyltritylamine. When both *N*-allyltritylamine and 1 eq. of DIPEA were simultaneously used in the reaction, the isomerization yield was improved dramatically to 80%. Furthermore, no self-metathesis product could be detected. The new catalytic system offers a novel procedure for the cleavage of allyl ethers/acetals to provide reducing sugars such as **199** (Scheme 35).



Scheme 35

Conclusions

The results outlined herein show that olefin metathesis has already proven to be an efficient method in synthetic organic chemistry. With the development of well-defined catalytic systems (**1**–**7**) and a better understanding of the nature of these catalysts, selective cross-metathesis, ring-closing metathesis and ring-opening metathesis reactions have started to appear in the literature. It has been shown that this efficient reaction provides diverse types of new alkenes, including some total syntheses of carbohydrate-containing natural products which can not be readily obtained by other known procedures, especially involving closure of large rings (macrocycles). While this review was under preparation, several other examples appeared in the literature[53–64] and we apologise to those investigators whose work could not be summarized herein. Ongoing work to search for even more active and tolerant metal complexes promises further interesting and useful work ahead.

Acknowledgements

We gratefully acknowledge financial support from NSERC for this work.

Notes and references

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